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(54) Title: THERAPEUTIC AEROSOL FORMULATIONS

(57) Abstract

Disclosed are self-propelled therapeutic aerosol compositions, and a process for the preparation thereof, comprising a micronized, water soluble, propellant insoluble homogeneous complex of a drug and an extender suspended in a propellant mixture.

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THERAPEUTIC AEROSOL FORMULATIONS

Background of the Invention

1. Field of the Invention

The present invention relates to a novel therapeutic self-propelled aerosol formulation for inhalation. More particularly, it relates to a therapeutic formulation of the dispersion or suspension type comprising: a physiologically active solid drug and a solid extender or carrier for the drug suspended in a chlorofluorocarbon propellant mixture.

The present invention also relates to a process for the preparation of self-propelled aerosol formulation intended for inhalation wherein the preparative steps include: dissolving a solid drug and a solid extender or carrier in a solvent; lyophilizing the solution to obtain a powder; micronizing and suspending the powder in a propellant mixture.

The preferred embodiment of the present invention relates to a self-propelled aerosol formulation for inhalation wherein the active drug is a polypeptide having calcitonin activity for the treatment of bone diseases.

Inhalation therapy involves direct deposition of medication onto the airway of a patient by the nasal or oral routes. This method of delivery of medication is therapeutically sound and is well accepted in the prior art. Among the benefits of the method are: the rapid medication

effects essential in the treatment of life threatening afflictions, such as certain allergic and asthmatic conditions; the reduction of systemic side effects; convenience and cost as compared to, for example, intravenous or intramuscular administration; and self-administration of certain drugs such as the pharmaceutically active peptides that cannot be taken orally for reason of decomposition in the gastrointestinal tract.

Inhalation therapy can be used for the treatment of a variety of diseases requiring physiologically active drugs such as insulin, calcitonin, interferons, vaccines, decongestants, antiasthmatics and the like.

2. Description of the Prior Art

Delivery of medication in aerosol form to a patient has been proved to be an important therapeutically sound module. Its effectiveness, however, is dependent upon several key factors including particle stability, adequate penetration and deposition into the respiratory tract, precise dosage to provide uniform results, and non-irritation to the tracheobronchial tree.

Particle penetration and deposition are believed to maximized by the use of a particle size range of from about 2 to about 10μ. Particles less than 2μ, although reach the alveoli, deposit minimally and are likely to be exhaled. Particles 10μ or greater do not enter the respiratory tract and are deposited in the oropharynx. Comminuting solid drugs to obtain the desired particle size range poses no problem in the prior art. However, the requirements of particle stability, precise dosage and non-irritation have not been, in general, quite satisfactorily met. Generally described, the heretofore proposed and/or utilized aerosol formulations, are micronized drug particles suspended in a propellant mixture. Customarily, the formulations also contain a surfactant, a solvent or a dispersing agent to prevent agglomeration or sedimentation of the suspended particles. Despite the

presence of these agents the drug particles tend to form agglomerates, floating flocculants or sedimentary precipitations during extended shelf-life resulting in destruction or clogging of the dispensing mechanism, and when administered, uneven distribution and non-uniform dosage of the drug in the tracheobronchial tree of the patient. In addition, certain solvents and surfactants tend to cause irritation on extended use of the formulations.

Another major problem associated with these type of formulations is the handling and metering of the microgram quantities of the active drug required for the intended therapeutic purpose. During the manufacturing process resulting in the metering of the drug into the dispensing containers the amounts metered varies because of adsorption, absorption and agglomeration factors. To minimize this problem and also to more closely reach the optimum size range of particle size, the prior art incorporates a biologically inert or compatible particulate agent into inhalable aerosol formulations such as into bronchodilator, steroid, and nicotine formulations. While this approach is suitable to substantially solve the metering and particle size problems, it also tends to result in an unhomogeneous mixture wherein the inert particles of the extender are not uniformly and intimately mixed with the active drug particles. The lack of homogeneity is dependent on the comminuting and mixing process and will vary even from batch to batch of the product made. Respective specific gravities of the drug and the extender used will also greatly influence the homogeneity of the finished product ultimately resulting in the delivery of non-uniform dosages. It is, therefore, an object of the present invention to provide self-propelled therapeutic aerosol formulations for oral and/or nasal applications which satisfy the above-discussed requirements. It is a further object of the invention to provide, as the preferred embodiment, calcitonin containing self-propelled aerosol formulations for the treatment of various bone diseases.

SUMMARY OF THE INVENTION

According to the present invention, there is provided a self-propelled therapeutic aerosol formulation for oral and/or intranasal application comprising:

a) from about 0.01 to about 5.0% w/w, and preferably from about 0.1 to about 3.0% w/w, of a homogeneous complex of at least one active drug and a pharmaceutically acceptable extender, wherein said active drug comprises from about 0.1 to about 25.0% w/w of said homogeneous drug/extender complex;

b) from about 0.1 to about 3.0% w/w of a solvent and/or surfactant; and

c) from about 92 to about 99.89% w/w of a pharmaceutically acceptable propellant mixture having a density of about 1.33 to about 1.40 gm/cc.

Wherein said homogeneous complex is insoluble in said propellant mixture and is present in the form of micronized solid particles of which at least 90% w/w has an effective particle diameter of about 2 to about 10μ and having a density of about 1.33 to about 1.40 gm/cc.

In preparing the therapeutic aerosol formulations of the present invention, the active drug and the pharmaceutically acceptable extender are dissolved in water, the resultant solution is lyophilized forming a homogeneous complex wherein the drug and extender molecules are in intimate contact with each other. The so obtained powder is comminuted to the desired particle size, then combined with a small amount of solvent and/or surfactant, followed by metering into aerosol containers and adding the propellant mixture thereto.

Detailed Description of the Invention

In accordance with the present invention, the desired self-propelled therapeutic formulations can be obtained as described above and as will be further explained and exemplified in detail.

Extenders

The extenders serve as carriers and diluents for the active drugs in the formulations and comprise about 75 to 99.9% of the drug/extender homogeneous complex. The extender must be a solid, water soluble, propellant insoluble, pharmaceutically acceptable material, so that it can be dissolved in an aqueous solution together with the active drug, lyophilized and the so obtained homogeneous complex comminuted to the desired particle size.

We have found the amino acid DL-Methionine to function extremely well in the formulations according to the present invention. However, other water soluble hydrocarbon insoluble pharmaceutically acceptable agents which are in, or can be made into, a solid form, are also applicable, such as:

a) other amino acids, including D or L-Methionine, glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, serine, cystein, aspartic acid, glutamic acid, arginine, lysine, asparagine, histidine, tryptophan and proline;

b) monosaccharides, such as, D-allose, D-altrose, fructose, galactose, glucose, inositol, D-mannose and sorbose;

c) disaccharides, such as, sucrose, cellobiose, lactose, maltose, melibiose, trehalose and turanose;

d) polysaccharides, such as, dextrin, glycogen and starch; and

e) peptides and proteins, such as the widely used dipeptide, Aspartame.

Solvents and/or Surfactants

The present invention utilizes from about 0.1 to about 3.0% w/w of a solvent and/or surfactant to help maintain a stable suspension. The solvents used include alcohols, preferably ethyl alcohol; while the surfactants include nonionic, cationic and anionic surface active agents, the preferred being oleic acid.

The Propellant Mixture

The propellant mixture comprises from about 92 to about 99.89% w/w of the total formulation having a density of about 1.33 to 1.40 gm/cc and consists of a 90/10 mixture of dichlorodifluoromethane and dichlorotetrafluoroethane, or a 90/10 mixture of dichlorodifluoromethane and trichlorofluoromethane, sold under the trade names Dymel 12, Dymel 114 and Dymel 11 respectively.

The Active Drugs

The active drug comprises from about 0.1 to about 25.0% w/w of the drug/extender homogeneous complex. Drugs in solid form and drugs that can be made into a solid form and are soluble in aqueous solutions and insoluble in the hydrocarbon mixtures hereindescribed are contemplated for use in accordance with the present invention.

While the invention is applicable to several pharmaceutically potent classes of drugs, it is especially suitable for delivery of bronchodilators, cardiovascular drugs, hormones and enzymes. Illustrative examples include bronchodilators, such as:

Ipratropium bromide = 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-

methyl-8-(1-methylethyl)-3-azonicabicyclo[3.2.1]octane bromide;

Metaproterenol sulfate = 5-[1-hydroxy-2-[(1-methylethyl)-amino]ethyl]1,3-benzenediol sulfate;

Terbutaline sulfate = 5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-1,3-benzenediol sulfate;

Bitolterol mesylate = 4-methylbenzoic acid 4-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-1,2-phenylene ester mesylate;

Isoproterenol hydrochloride = 4-[1-hydroxy-2-[(1-methyl-ethyl)amino]ethyl]-1,2-benzenediol hydrochloride;

Epinephrine hydrochloride = 4-[1-hydroxy-2(methylamino)-ethyl]-1,2-benzenediol hydrochloride;

Albuterol sulfate = α'-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol sulfate; and

Theophylline = 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione.

Cardiovascular drugs, such as:

Clonidine hydrochloride = 2,6-dichloro-N-2-imidazolidinyli-denebenzeneamine hydrochloride;

Terazosin hydrochloride = 1-(4-amino-6,7-dimethoxy-2-quina-zolinyl)-4[(tetrahydro-2-furanyl)carbonyl)]piperazine hydrochloride;

Prazosin hydrochloride = 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)piperazine hydrochloride;

Tolazoline hydrochloride = 4,5-dihydro-2-(phenylmethyl)-1H-imidazole monohydrochloride;

Labetalol hydrochloride = 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide monohydrochloride;

Captopril = 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline;

Verapamil hydrochloride = α-[3-[[2-(3,4-dimethoxyphenyl)-ethyl]-methylamino]propyl]-3,4-dimethoxy-α(1-methylethyl)benzene-acetonitrile hydrochloride;

Diltiazem hydrochloride = 3-(acetyloxy)-5-[2-(dimethylmino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride;

Propranolol hydrochloride = 1-(isopropylamino)-3-(1-napthyl-oxy)-2-propanol hydrochloride;

Bretylium tosylate = (o-bromobenzyl) ethyl dimethylammonium p-toluene solfonate;

Lidocaine hydrochloride = 2-(diethylamino)-2',6'-acetoxyl-idide monohydrochloride;

Mexilitine hydrochloride = 1-methyl-2-(2,6-xylyloxy)-ethyl-amine hydrochloride;

Disopyramide phosphate = α-[2-diisopropylamino)ethyl]-α-phenyl-2-pyridineacetamide phosphate;

Procainamide hydrochloride = p-amino-N-[2-(diethylamino)-ethyl]-benzamide hydrochloride;

Flecainide acetate = N-(2-piperidinylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide monoacetate;

Tocainide hydrochloride = 2-amino-N-(2,6-dimethylphenyl)-propanamide hydrochloride;

Methoxamine hydrochloride = α-(1-aminoethyl)-2,5-dimethoxy-benzenemethanol hydrochloride;

Minoxidil = 6-(1-piperidinyl)-2,4-pyrimidinediamine-3-oxide;

Metoprolol tartrate = 1-(isopropylamino)-3-[p-(2-methoxy-ethyl)phenoxy]-2-propanol (2:1) dextro-tatrate salt;

Hydroflumethiazide = 3,4-dihydro-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide;

Amrinone lactate = 5-amino[3,4'-bipyridine]-6(1H)-one lactate;

Ethaverine hydrochloride = 1-[(3,4-diethoxyphenyl)methyl]-6,7-diethoxyisoquinoline hydrochloride; and

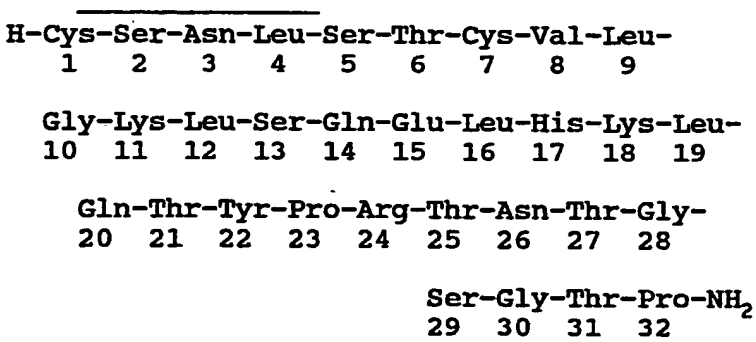
Papaverine hydrochloride = 1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline hydrochloride.

The preferred embodiment of the invention utilizes calcitonin as the active polypeptide for the treatment of bone diseases.

Calcitonin

Calcitonin is a polypeptide hormone involved in the control of calcium metabolism in the body. All known natural calcitonin peptides contain an amino acid sequence of 32 amino acids, of which the seven at the amino terminal end of the

peptide chain are held in a cyclic configuration by a sulphur or carbon bridge and the carboxyl terminal residue consists of proline amide. The natural calcitonins include the salmon, eel, bovin, porcine, ovine, rat and human calcitonin. The detailed structure within the peptide chain of the hormone varies among different species and while the hormones, and their derivatives and analogues found in various species are of interest for use in the present invention, salmon calcitonin is of special interest in view of its relatively hydrophilic character and its stability. Salmon calcitonin has the following formula:



In U.S. Pat. Nos. 3,926,938, 4,062,815, 3,929,758, 4,033,940, 4,336,187, 4,388,235, 4,391,747 and 4,401,593 are disclosed improved synthesis of calcitonin including the salmon calcitonin referred to above.

Human, salmon and porcine calcitonin have been available for therapeutic use for several years. For example, synthetic salmon calcitonin is marketed by Armour Pharmaceutical Co. under the tradename CALCIMAR in a sterile, lyophilized form reconstitutable for subcutaneous or intravascular injection for the treatment of bone diseases.

The level of hypocalcemic activity of calcitonin varies from species to species. Salmon and chicken calcitonin have a potency of about 4,000 to 6,000 MCR (Medical Research Council) U/mg peptide; eel calcitonin about 2,000 to 4,000 MRC U/mg peptide; rat 400 MRC U/mg; while beef, sheep, hog and man about 100 to 200 MRC U/mg peptide.

Calcitonin used by the present invention may be obtained from Armour Pharmaceutical Co., from natural sources, or by synthetic routes known in the art. The synthesis can be performed by classical peptide synthesis as well as by solid phase synthesis.

In addition to the above-described calcitonin, the present invention encompasses synthetic calcitonin peptides having biological activity of the same type as those above-described. Such synthetic calcitonin are disclosed, along with processes for preparation thereof in the following U.S. Pat. Nos.

4,388,235	4,604,238
4,391,747	4,605,514
4,397,780	4,605,515
4,401,593	4,606,856
4,414,149	4,622,386
4,444,681	4,622,387
4,451,395	4,622,388
4,469,636	4,632,978
4,497,731	4,639,509
4,497,732	4,639,510
4,528,132	4,639,511
4,537,716	4,650,854
4,597,900	4,659,804
4,604,236	4,732,969
4,604,237	4,746,728

Synthetic calcitonin analogues disclosed in these patents are incorporated herein by reference as if set out in full herein. This list is not intended to be exhaustive of all U.S. Patents covering synthetic calcitonin analogues, but is representative of the analogues useful in the present invention; nor is the invention limited to the compounds disclosed in the listed patents.

In accordance for the foregoing, the following analogues of calcitonin constitute specific active ingredients used in

the various suppository formulations of the present invention:

1. Des Asparagine-3-Calcitonin having the structures:

(a) H-Cys-Ser-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2; and

(b) Cys-Ser-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2.

2. [16-Alanine] Calcitonin having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon);

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2 (Eel); and

(c) Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-Thr-Tyr-Thr-Gln-Asp-Ala-Asn-Lys-Phe-His-Thr-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro-NH_2 (Human).

3. Des ^{2}-Glycine ^{8}-Des ^{22}-Calcitonin having the structures:

(a) H-Cys-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon); and

(b) H-Cys-Asn-Leu-Ser-Thr-Cys-Gly-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-
Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asp-
Val-Gly-Ala-Gly-Thr-Pro-Nh_2 (Eel).

4. Des-13-Serine-Calcitonin having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Gly-Thr-Pro-NH_2;

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-
Gly-Thr-Pro-NH_2; and

(c) Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-
Thr-Tyr-Gln-Asp-Phe-Asn-Lys-Phe-His-
The-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-
Gly-Ala-Pro-NH_2.

5. Des-21-Threonine-Calcitonin having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-
Pro-NH_2 (Salmon);

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-
Pro-NH_2, (Eel); and

(c) Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-
Thr-Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-
Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-
Pro-NH_2 (Human).

6. [Gly^2, Ser^3, Gly^8, des-Tyr^{22}] Calcitonin having the following structures:

(a) Cys-Gly-Ser-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2; and

(b) Cys-Gly-Ser-Leu-Ser-Thr-Cys-Gly-Lue-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2.

7. Des-4-Leucine-Calcitonin having the following structures:

(a) Cys-Ser-Asn-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon);

(b) Cys-Ser-Asn-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2 (Eel); and

(c) Cys-Gly-Asn-Ser-Thr-Cys-Met-Leu-Gly-Thr-Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-Thr-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro-NH_2 (Human).

8. Calcitonin-(1-23)-Peptide Amides having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-NH_2; and

(b) R_1 R_2
Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-NH_2.

9. [Des-1-Amino,8-Glycine) Calcitonin having the following structures:

(a) Bmp-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2 (Salmon); and

(b) Bmp-Scr-Asn-Leu-Scr-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Scr-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-
Thr-Pro-NH_2 (Eel).

10. [1,7-Di-Alanine] Calcitonin having the following structures:

(a) Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2; and

(b) Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-
Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-
Gly-Thr-Pro-NH_2.

11. 8-Methionine Calcitonin having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Met-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-
Gly-Ser-Gly-Thr-Pro-NH_2; and

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Met-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-

Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-
Gly-Ala-Gly-Thr-Pro-NH_2.

12. Des-2-Serine, 3-Asparagine Calcitonin having the following structures:

(a) Cys-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Gly-Thr-Pro-NH_2; and

(b) Cys-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Scr-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-
Gly-Thr-Pro-NH_2.

13. G-Serine, Des-19-Leucine Calcitonin having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Gly-Thr-Pro-NH_2; and

(b) Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-
Gly-Lys-Leu-Scr-Gln-Glu-Leu-His-Lys-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-
Thr-Pro-NH_2.

14. [16,19-Di-Alanine] Calcitonin having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Ala-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2; and

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Ala-Gln-

Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-
Thr-Pro-NH_2.

15. (1-S-Acetamidomethyl Cysteine, 7-Alanine) Calcitonin having the following structures:

(a) $SCH_2NH-C(O)-CH_3$
Cys-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2; and

(b) $SCH_2NH-C(O)-CH_3$
Cys-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-
Thr-Pro-NH_2.

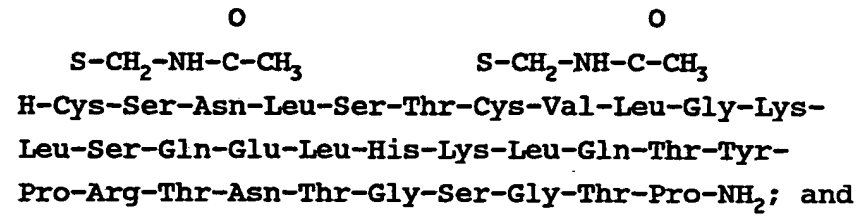
16. Des-19-Leucine - Calcitonin Analogs having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-
Ser-Gly-Thr-Pro-NH_2; and

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-
Ala-Gly-Thr-Pro-NH_2.

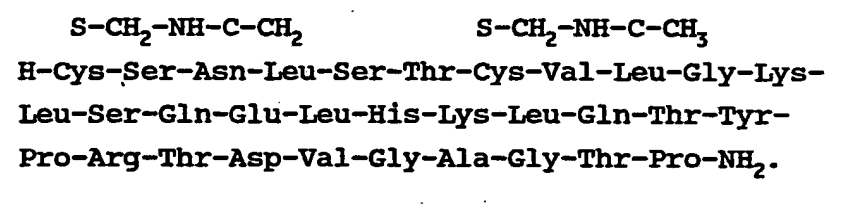
17. (Bis-1,7-S-Acetamidomethyl-L-Cysteine) Salmon Calcitonin having the following structures:

(a)



H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2; and

(b)



H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2.

18. 8-Glycine, Des-19-Leucine-Calcitonin having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon);

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2 (Eel); and

(c) Cys-Ala-Ser-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2 (Chicken).

19. Des-Leu^{16}-Calcitonin having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon);

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-His-Lys-Leu-Gln-

Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-
Gly-Thr-Pro-NH_2 (Eel); and

(c) Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-
Thr-Tyr-Thr-Gln-Asp-Asn-Lys-Phe-His-
Thr-Phe-Pro-Glu-Thr-Ala-Ile-Gly-Val-
Gly-Ala-Pro-NH_2 (Human).

20. Leucine^{22} - Calcitonin having the following structures:

(a) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-
Leu-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
NH_2 (Salmon); and

(b) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Leu-Pro-
Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2 (Eel).

21. Glycine - 8 Calcitonin having the following structures:

(a) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2; and

(b) Cys-Gly-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Thr-Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-Thr-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro-NH_2.

22. Glycine^{8}-D-Arginine^{24} Calcitonin having the following structures:

(a) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-D-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon); and

(b) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-D-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2 (Eel).

23. L-Tyrosine^{21} Calcitonin having the following structures:

(a) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Tyr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon); and

(b) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-

Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Leu-Gln-Tyr-Tyr-Pro-Arg-Thr-Asp-Val-
Gly-Ala-Gly-Thr-Pro-NH_2 (Eel).

24. D-Arginine^{24} Calcitonin having the following structures:

(a) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Leu-Gln-Thr-Tyr-Pro-D-Arg-Thr-Asn-Thr-
Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon); and

(b) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Leu-Gln-Thr-Tyr-Pro-D-Arg-Thr-Asp-Val-
Gly-Ala-Gly-Thr-Pro-NH_2 (Eel).

25. Amides Analogues of Calcitonin having the following structures:

(a) Y-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
1 2 3 4 5 6 7 8 9 10

X X
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-
11 12 13 14 15 16 17 18 19 20 21

X
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2
22 23 24 25 26 27 28 29 30 31 32

wherein Y is N(a) decanoyl and X is N(e) decanoyl.

26. [N-alpha, 1,7-Di-Alanine, Des-19-Leucine] Calcitonin having the following structures:

(a) [N-alpha-X, 1, 7 Di-Alanine (8-Y) Des-19-Leucine] calcitonin, wherein X is H, free amino or acyl-amino wherein acyl is derived from a carboxylic acid having 1-10 carbon atoms, L-lactic acid or half amide of malonic, succinic, glutaric, or adipic acids; Y is L-valine, glycine, L-methionine, L-alanine, L-leucine or L-isoleucine; and

(b) [N-alpha-X, 1, 7-Di-Alanine, Des-19-Leucine] calcitonin, wherein X is an acyl derived from carboxylic acid having 1-5 carbon atoms.

27. 1,7-Di-Alanine, 8-Glycine, Des-19-Leucine Calcitonin having the following structure:

H_2N-Ala-Ser-Asn-Leu-Ser-Thr-Ala-Gly-Leu-Gly-Lys-
1 5 10
Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-Arg-
15 20
Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-(C=O)-NH_2.
25 30

28. Nα-Propionyl, 1,7-Di-Alanine, Des-19-Leucine Calcitonin having the following structure:

CH_3-CH_2-(C=O)-Hn-
Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
1 5 10
Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-
15 20
Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-(C=O)-NH_2.
25 30

Preparation of the Formulations

In accordance with the present invention, the active drug and the extender, both being in a solid form, are dissolved in water by means of mechanical mixing, followed by lyophilization and comminution to the desired particle size, using well-known technique employed in the prior art. The drug/extender complex, at least 90% of which possess an effective particle diameter of about 2 to 10 μ is combined with a solvent or surfactant by means of blending and metered into a suitable aerosol container. Lastly, the desired amount of the 90/10 dichlorodifluoromethane/ dichlorotetrafluoroethane is charged into the container to complete the process in making the self-propelled formulation.

Preparative examples and typical formulations are set forth below, however, it is to be understood that these examples are given by way of illustration only and are not to be construed as limiting the invention either in spirit or in scope as many modifications will be apparent to those skilled in the art.

EXAMPLE 1

99.25 grams of DL-Methionine and 0.75 grams of salmon calcitonin (4848 MRC unit/mg) were dissolved in 5.5 liters of deionized water. The resultant solution was lyophilized, and the powder was micronized. An analysis of the micronized powder showed the presence of 0.74% w/w calcitonin and 101.15% w/w DL-Methionine.

The micronized calcitonin/DL-Methione complex was then combined with oleic acid and a 90/10 blend of Dymel 12/Dymel 114 in a suitable container. The so prepared formulation was found to contain:

0.250 grams of calcitonin/DL-Methionine;
0.095 grams of oleic acid; and
16.023 grams of 90/10 Dymel 12/Dymel 114.

Dose delivery was found to contain an average of 7.32μg of calcitonin and 1063μg DL-Methionine per actuation, while content uniformity was found to be an average of 1.795μg/unit of calcitonin and 259.2μg/unit DL-Methionine. Particle size measurement showed an M50 of 4.4μ and an M90 of 13.5μ.

EXAMPLE 2

95.5 grams of DL-Methionine and 4.5 grams of salmon calcitonin were dissolved in 5.5 liters of deionized water. The solution was lyophilized and the so obtained powder was micronized. The calcitonin/DL-Methionine complex was then processed as in Example 1. Dose delivery measurement showed 45 mg of calcitonin and 955 mg DL-Methionine per actuation.

EXAMPLE 3

A calcitonin/DL-Methionine complex was prepared and processed as in Example 1. The final formulation contained 0.125 grams of calcitonin/DL-Methionine, 0.095 grams of oleic acid and 16.148 grams of 90/10 mixture of Dymel 12/Dymel 114.

Dose delivery was found to be 22.5μg of calcitonin and 477.5μg of DL-Methionine per actuation.

EXAMPLE 4

16.0 grams of DL-Methionine and 4.0 grams of salmon calcitonin (having calcitonin activity of 4000 MRC unit/mg)

were dissolved in one liter of deionized water. The resultant solution was lyophilized and the powder was micronized. A slurry was prepared consisting of 20.0 grams of DL-Methionine/SCT, 40.0 grams of absolute ethanol, and 40.0 grams of oleic acid. 250 ml of the slurry was then combined with 9.75 ml of 90/10 of Dymel 12/Dymel 114 propellant blend to produce the following self-propelled aerosol suspension:

Ingredients	Volume (ml)
DL-Methionine	0.050
Ethanol, absolute	0.100
Oleic acid	0.100
90/10 Dymel 12/Dymel 114	9.750
Total	10.000

The formulation provides 200 IU/50μL per actuation.

EXAMPLE 5

5.62 grams of triamcinolone acetonide (a steroidal hormone/anti-inflammatory agent) and 23.0 grams of L-alanine were dissolved in 1.5 liters of deionized water. The resultant solution was lyophilized and the powder micronized

and sifted to meet particle size requirements. A slurry was then prepared using the micronized powder, 15 grams of SPAN 85 and 120 grams of ethanol. The slurry was then combined with a propellant mixture containing 3,000 grams of Dymel 114 and 12,000 grams of Dymel 12. The formulation had the following composition:

Ingredients	Composition in % w/w
Triamcinolone acetonide	0.037
L-alanin	0.152
SPAN 85	0.099
Ethanol, absolute	0.792
Dymel 12	79.151
Dymel 114	19.769
Total	100.000

Lung absorption studies conducted on Sprague-Dawley rats using calcitonin formulations of the present invention showed highly significant hypocalcemic responses over that of the placebo.

While only certain embodiments of our invention have been

described in specific detail, it will be apparent to those skilled in the art that many other specific embodiments may be practiced and many changes may be made all within the spirit of the invention and the scope of the appended claims.

WHAT WE CLAIM IS:

1. A self-propelled therapeutic aerosol suspension for inhalation comprising: from about 0.01 to about 5.0% w/w of a water soluble, propellant insoluble solid homogeneous complex in micronized form of at least one active drug and a pharmaceutically acceptable extender, wherein said active drug comprises from about 0.1 to about 25.0% w/w of said homogeneous drug/extender complex;

   from about 0.1 to about 3.0% w/w of a solvent and/or surfactant; and

   from about 92.0 to about 99.89% w/w of a pharmaceutically acceptable propellant mixture.

2. The self-propelled therapeutic aerosol suspension of claim 1 for oral application.

3. The self-propelled therapeutic aerosol suspension of claim 1 for intranasal application.

4. The self-propelled therapeutic aerosol suspension of claim 1 wherein at least 90% of said homogeneous complex

in micronized form has an effective particle diameter of about 2 to about 10μ.

5. The self-propelled therapeutic aerosol suspension of claim 1 wherein said propellant mixture essentially consists of about 90% w/w dichlorodifluoromethane and about 10% w/w dichlorotetrafluoroethane, or about 90% w/w dichlorodi-
fluoromethane and about 10% w/w trichlorofluoromethane.

6. The self-propelled therapeutic aerosol suspension of claim 1 wherein said propellant mixture has a density of about 1.33 to about 1.40 gm/cc.

7. The self-propelled therapeutic aerosol suspension of claim 1 wherein said extender is selected from the group consisting of amino acids, monosaccharides, disaccharides, polysaccharides, peptides and proteins.

8. The self-propelled therapeutic aerosol suspension of claim 1 wherein said extender is DL-Methionine.

9. The self-propelled therapeutic aerosol suspension of claim 1 wherein said solvent is ethanol.

10. The self-propelled therapeutic aerosol suspension of claim 1 wherein said surfactant is oleic acid.

11. The self-propelled therapeutic aerosol suspension of claim 1 wherein said active drug is selected from the group consisting of bronchodilators, cardiovascular drugs, hormones and enzymes.

12. The self-propelled therapeutic aerosol suspension of claim 1 wherein said active drug is a polypeptide.

13. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is selected from the group consisting of eel, bovine, porcine, ovine, rat, chicken and human calcitonin.

14. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is salmon calcitonin.

15. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is obtained from natural sources.

16. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is obtained by a

synthetic route.

17. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide has a potency of from about 100 to about 10,000 international units per mg of polypeptide.

18. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is [N-alpha-X, 1,7 Di-Alanine (8-Y) Des-19-Leucine] calcitonin, wherein X is H, free amino or acyl-amino wherein acyl is derived from a carboxylic acid having 1-10 carbon atoms, L-lactic acid or half amide of malonic, succinic, glutaric, or adipic acids; and Y is L-valine, glycine, L-methionine, L-alanine, L-leucine or L-isoleucine.

19. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is [N-alpha-X, 1,7-Di-Alanine, Des-19-Leucine] calcitonin, wherein X is an acyl derived from carboxylic acid having 1-5 carbon atoms.

20. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-

Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-
Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

21. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2 (Salmon).

22. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Asn-Leu-Ser-Thr-Cys-Gly-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-
Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asn-
Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

23. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-

Gly-Thr-Pro-NH_2.

24. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

25. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Gly-Ser-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

26. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

27. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-
Gln-Thr-Tyr-Pro-NH_2.

28. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Bmp-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2 (Salmon).

29. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

30. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

31. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

32. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

R_1 R_2

Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2; where R_1 is S-n-alkyl, Cys or H and R_2 is S-n-alkyl or H, R_1 being S-n-alkyl, Cys or H when R_2 is H and R_2 being S-n-alkyl or H when R_1 is H.

33. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Gly-Thr-Pro-NH_2.

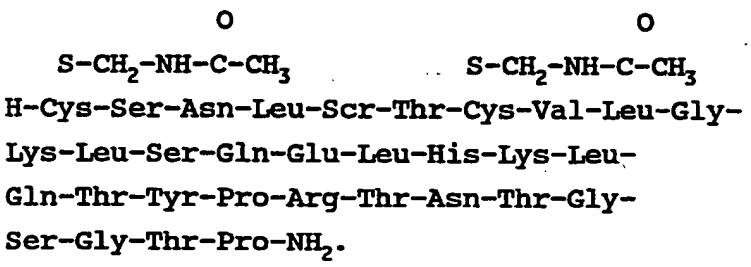
34. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

$SCH_2NH-C(O)-CH_3$
Cys-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2.

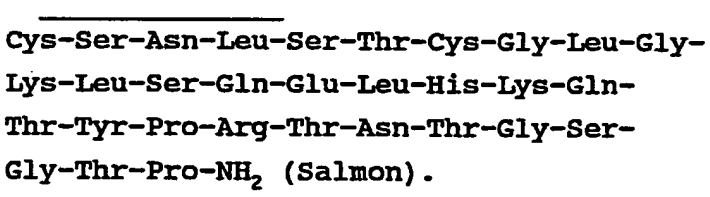
35. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-
Ser-Gly-Thr-Pro-NH_2.

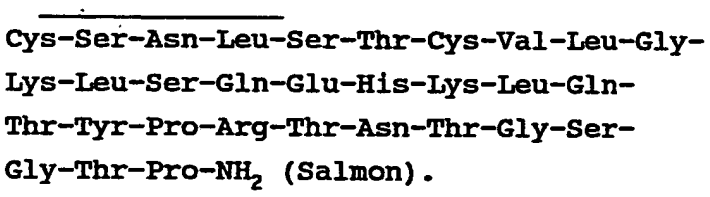
36. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:



37. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:



38. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:



39. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Leu-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

40. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

41. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-D-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

42. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-
Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-
His-Lys-Leu-Gln-Tyr-Tyr-Pro-Arg-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

43. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-D-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2 (Salmon).

44. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

```
Y-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
  1   2   3   4   5   6   7   8   9   10
 X                               X
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-
11  12  13  14  15  16  17  18  19  20  21
          X
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH2
22  23  24  25  26  27  28  29  30  31  32
```

wherein Y is N(a) decanoyl and X is N(e) decanoyl.

45. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H_2N-Ala-Ser-Asn-Leu-Ser-Thr-Ala-Gly-Leu-Gly-Lys-
1 5 10
Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-Arg-
15 20
Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-(C=O)-NH_2.
25 30

46. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

$CH_3-CH_2-(C=O)-Hn-$

Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
1 5 10

Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-
15 20

Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-$(C=O)-NH_2$.
25 30

47. A method for the treatment of a patient suffering from diseases of hyperparathyroidism, idiopathic hypercalcemia of infancy, Paget's disease, vitamin D intoxication, or osteolytic bone metastases, said diseases characterized by hypercalcemia and high phosphate concentrations in the blood of said patient comprising: administering to said patient in need of such treatment to effect control of at least one of said diseases an effective amount of the composition of claim 12.

48. A method of making a self-propelled aerosol suspension for inhalation comprising the steps of:

dissolving a solid active drug and a solid pharmaceutically acceptable extender in an aqueous solution;
lyophilizing said solution to form a solid, homogeneous complex of said drug and said extender in the form of a

powder;

comminuting said powder to obtain a particle size of which at least 90% has an effective diameter of about 2 to about 10μ;

combining said particles with a small amount of a solvent and/or surfactant; and adding an aerosol propellant mixture thereto consisting of 90% w/w dichlorodifluoromethane and 10% w/w dichlorotetrafluoroethane, or 90% w/w dichlorodifluoromethane and 10% w/w trichlorofluoromethane.

AMENDED CLAIMS

[received by the International Bureau on 20 August 1990 (20.08.90); original claims 20-28,30,31,33,35-44 amended;other claims unchanged (9 pages)]

17. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide has a potency of from about 100 to about 10,000 international units per mg of polypeptide.

18. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is [N-alpha-X, 1,7 Di-Alanine (8-Y) Des-19-Leucine] calcitonin, wherein X is H, free amino or acyl-amino wherein acyl is derived from a carboxylic acid having 1-10 carbon atoms, L-lactic acid or half amide of malonic, succinic, glutaric, or adipic acids; and Y is L-valine, glycine, L-methionine, L-alanine, L-leucine or L-isoleucine.

19. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is [N-alpha-X, 1,7-Di-Alanine, Des-19-Leucine] calcitonin, wherein X is an acyl derived from carboxylic acid having 1-5 carbon atoms.

20. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-

Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-
Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

21. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2 (Salmon).

22. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Asn-Leu-Ser-Thr-Cys-Gly-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-
Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asn-
Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

23. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-

Gly-Thr-Pro-NH_2.

24. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-
Pro-NH_2 (Salmon).

25. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Gly-Ser-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-
Pro-NH_2.

26. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-
Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
NH_2 (Salmon).

27. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-
Gln-Thr-Tyr-Pro-NH_2.

28. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Bmp-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2 (Salmon).

29. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

30. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Met-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-
Gly-Ser-Gly-Thr-Pro-NH_2.

31. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Gly-Thr-Pro-NH_2.

32. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

R_1 R_2
Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-Lys-Leu-
Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-Arg-Thr-
Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2; where R_1 is S-n-alkyl, Cys or H and R_2 is S-n-alkyl or H, R_1 being S-n-alkyl, Cys or H when R_2 is H and R_2 being S-n-alkyl or H when R_1 is H.

33. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Gly-Thr-Pro-NH_2.

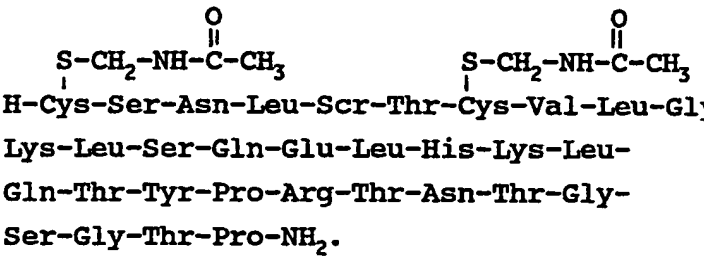
34. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

$SCH_2NH-C(O)-CH_3$
Cys-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2.

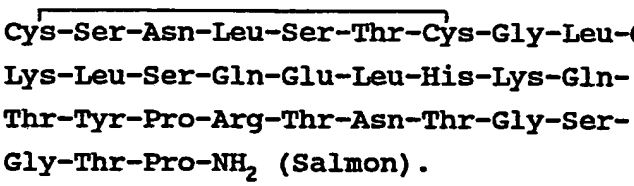
35. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-
Ser-Gly-Thr-Pro-NH_2.

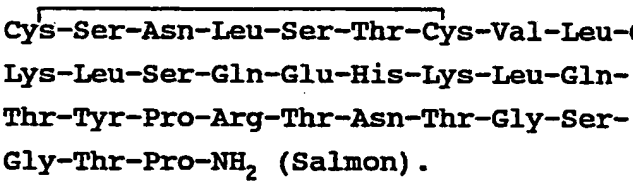
36. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:



37. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:



38. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:



39. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Leu-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

40. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

41. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-D-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

42. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-
Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-
His-Lys-Leu-Gln-Tyr-Tyr-Pro-Arg-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon).

43. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-D-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
Thr-Pro-NH_2 (Salmon).

44. The self-propelled therapeutic aerosol suspension of claim 12 wherein said polypeptide is:

```
Y-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
  1   2   3   4   5   6   7   8   9   10
 X                             X
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-
11  12  13  14  15  16  17  18  19  20  21
         X
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH2
22  23  24  25  26  27  28  29  30  31  32
```

wherein Y is N(a) decanoyl and X is N(e) decanoyl.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/00928

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5) A61K 9/12,37/02; C07K 7/50
(USCL) 424/40, 514/12.13; 530/307,324

II FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
US	424/40; 514/12,13; 530/307,324

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
X,P	US, A, 4,895,719 (RADHAKRISHNAN) 23 January 1990 see cols 7-8 and col 10	1-48
Y	US, A, 4,758,550 (CARDINAUX ET AL.) 19 July 1988 see col 16 and claims	1-48
X	US, A, 4,788,221 (KAGATANI ET AL.) 29 November 1988 see col 2 and abstract	1-48
X	US, A, 4,690,952 (KAGATANI ET AL.) 01 September 1987 see col 2 and claims	1-48
A	US, A, 4,241,051 (CHRISTIE ET AL.) 23 December 1980 see entire document	1-48

* Special categories of cited documents: 10

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11 MAY 1990	20 JUN 1990
International Searching Authority	**Signature of Authorized Officer**
ISA/US	LESTER L. LEE

Form PCT/ISA/210 (second sheet) (Rev.11-87)